Protocol Title: Effect of PTH analog on union rates of Type II odontoid fractures in older adults
ClinicalTrials.gov ID: NCT04760782
Principal Investigator: David Lunardini

Attachments:

1. **Protocol** (Version Date 16Mar2023, IRB-approved 13Apr2023)
2. **Informed Consent Form, Treatment Group** (Version Date 16Mar2023, IRB-approved 13Apr2023)
3. **Informed Consent Form, Historical Control Group (Active Control Participants).** Version Date 25May2022, IRB-approved 28May2022)

Human Subjects Research Protocol

PROTOCOL SUMMARY

Project Title:	**Protocol Version Date (required for each protocol modification):**
Effect of PTH analog on union rates of Type II odontoid fractures in older adults	16Mar2023

Principal Investigator: David Lunardini

TYPE OF REVIEW

Which type of IRB review are you requesting? Full [ ] Expedited [X] Complete category.

Your research may be expeditable if the research activities (1) present no more than minimal risk to human subjects, and (2) involve only procedures listed in one or more of the following categories: (CHECK THE CATEGORY(IES) THAT APPLY.

[X] (1) **Clinical studies of drugs and medical devices only when condition (a) or (b) is met.**

(a) Research on drugs for which an investigational new drug application (21 CFR Part 312) is not required. (NOTE: Research on marketed drugs that significantly increases the risks or decreases the acceptability of the risks associated with the use of the product is not eligible for expedited review).

(b) Research on medical devices for which (i) an investigational device exemption application (21 CFR Part 812) is not required; or (ii) the medical device is cleared/approved for marketing and the medical device is being used in accordance with its cleared/approved labeling.

[X] (2) **Collection of blood samples** by finger stick, heel stick, ear stick, or venipuncture as follows: (a) from healthy, non-pregnant adults who weigh at least 110 pounds. For these subjects, the amounts drawn may not exceed 550 ml in an 8 week period and collection may not occur more frequently than 2 times per week: or (b) from other adults and children, considering the age, weight, and health of the subjects, the collection procedure, the amount of blood to be collected, and the frequency with which it will be collected. For these subjects, the amount drawn may not exceed the lesser of 50 ml or 3 ml per kg in an 8 week period and collection may not occur more frequently than 2 times per week.

[ ] (3) Prospective **collection of biological specimens** for research purposes by noninvasive means.

[ ] (4) **Collection of data through noninvasive procedures** (not involving general anesthesia or sedation) routinely employed in clinical practice, excluding procedures involving x-rays or microwaves.

[X] (5) Research involving **materials** (data, documents, records, or specimens) that have been collected, or will be **collected solely for nonresearch purposes** (such as medical treatment or diagnosis). (NOTE: Some research in this category may be exempt from the HHS regulations for the protection of human subjects. 45 .CFR 46.101 (b)(4). This listing refers only to research that is not exempt.)

[ ] (6) **Collection of data from voice, video, digital, or image recordings** made for research purposes.

[ ] (7) **Research on individual or group characteristics or behavior or research employing survey, interview, oral history, focus group, program evaluation, human factors evaluation, or quality assurance methodologies.** (NOTE: Some research in this category may be exempt from the HHS regulations for the protection of human subjects. 45 CFR 46.101(b)(2) and (b)(3)).

PURPOSE AND OBJECTIVES

Purpose: The importance of the research and the potential knowledge to be gained should be explained in detail. Give background information.

Odontoid fractures are the most common spinal fracture in elderly patients. Type II fractures which involve the waist of the dens are the most common, but heal least reliably due the watershed vascularity of this area, as well as low intrinsic stability of common fracture patterns. Non-union after non-operative treatment is even more prevalent (up to 85%) in an elderly population. Odontoid non-union can be a source of neck pain and disability, and less commonly cervical spine instability or progressive myelopathy/neurologic decline. Operative treatment with C1-2 fusion restores spinal stability and leads to more reliable union rates (>90%); however, major

perioperative complications occur in ~40% of patients[1]. Given the significant morbidity and mortality associated with both operative and non-operative modalities, treatment of type II odontoid fractures in the elderly remains controversial.

Recent data from the AO Spine North American Geriatric Odontoid fracture study has suggested a survival benefit, particularly for younger elderly patients, who undergo operative stabilization of their odontoid fracture[2]. The reason for this isn't fully understood, but is presumed to derive from achievement of stable bony union and its positive effect on pain, function, and possibly neurologic protection. If this stable bony union were able to be achieved more reliably without the risks of surgery in such a fragile population, that would represent a major advancement in care.

Parathyroid hormone analogs (e.g. teriparatide or abaloparatide) have been shown in multiple animal fracture models to have an anabolic effect on bone healing, however existing clinical data to date has produced conflicting results[3]. Peichl, et al. (2011) showed faster radiographic union rates in pubic bone fractures treated with PTH (7.6 wks) vs. control (12.8 wks), and Aspenberg et al. (2010) showed faster radiographic healing of distal radius fractures compared to placebo with 20ug dosing but no effect with 40ug dosing[4,5]. A further study looking at femoral neck fractures did not show similar treatment effects with PTH treatment[6]. There remains significant uncertainty about which fracture types may respond to treatment, as well as the dose-response relationship.

There has been no formal investigation into use of PTH for spinal fractures, though two case reports document four patients with chronic odontoid nonunion and pain who responded clinically and radiographically to a short course of teriparatide[7,8].

The purpose of this study is to prospectively study the effects of PTH analogs on the union rates of type II odontoid fractures in older adults as compared to a historical comparison group of patients treated with rigid immobilization alone. Our primary hypothesis is that the addition of PTH analog treatment to standard treatment with hard cervical collar will lead to higher rates of union when compared to treatment with hard cervical collar alone. If true, this could improve outcomes and alter the standard of care for these common and difficult to treat fractures, lessening the need to consider surgery in this high-risk patient population.

References. Include references to prior human or animal research and references that are relevant to the design and conduct of the study.

1. White AP, Hashimoto R, Norvell DC, Vaccaro AR. (2010) Morbidity and mortality related to odontoid fracture surgery in the elderly population. *Spine 35(9 Suppl): S146-57.*
2. Chapman J, Smith JS, Kopjar B, Vaccaro AR, Arnold P, Shaffrey CI, Fehlings MG. (2013) The AOSpine North America Geriatric Odontoid Fracture Mortality Study: a retrospective review of mortality outcomes for operative versus nonoperative treatment of 322 patients with long-term follow-up. *Spine* 38(13):1098-104.
3. Lanske, B., Chandler, H., Pierce, A., Brown, J., Ominsky, M., Kostenuik, P., & Hattersley, G. (2019). Abaloparatide, a PTH receptor agonist with homology to PTHrP, enhances callus bridging and biomechanical properties in rats with femoral fracture. *Journal of Orthopaedic Research*, *37*(4), 812-820.
4. Peichl, P., Holzer, L. A., Maier, R., & Holzer, G. (2011). Parathyroid hormone 1-84 accelerates fracture-healing in pubic bones of elderly osteoporotic women. *JBJS*, *93*(17), 1583-1587.
5. Aspenberg, P., Genant, H. K., Johansson, T., Nino, A. J., See, K., Krohn, K., ... & Mitlak, B. H. (2010). Teriparatide for acceleration of fracture repair in humans: a prospective, randomized, double-blind study of 102 postmenopausal women with distal radial fractures. *Journal of Bone and Mineral Research*, *25*(2), 404-414.
6. Bhandare M, Jin L, See K, Burge R, Gilchrist N, Witvrouw R, Krohn KD, Warner MR, Ahmad QI, Mitlak B. (2016) Does Teriparatide Improve Femoral Neck Fracture Healing: Results From A Randomized Placebo-controlled Trial. *Clin Orthop Relat Res 474(5):1234-44.*
7. Rubery, P. T., & Bukata, S. V. (2010). Teriparatide may accelerate healing in delayed unions of type III odontoid fractures: a report of 3 cases. *Clinical Spine Surgery*, *23*(2), 151-155.
8. Pola, E., Pambianco, V., Colangelo, D., Formica, V. M., Autore, G., & Nasto, L. A. (2017). Teriparatide anabolic therapy as potential treatment of type II dens non-union fractures. *World journal of orthopedics*, *8*(1), 82.

Additional references are listed under both 'Study Design' and 'Risks/Benefits' of the Methods and Procedures, below.

Objectives: Clearly state the primary and secondary objective(s) of the study.

Objective is to prospectively compare the union rate of type II odontoid fractures in older adults who are treated with a rigid cervical collar versus a rigid cervical collar plus PTH analog

METHODS AND PROCEDURES

Study Design: Describe the research design, including a description of any new methodology and its advantage over existing methodologies.

This is a prospective cohort study with a historical control group involving patients >=50 years-old with an acute (<3 weeks) Anderson & D'Alonzo type II dens fractures identified on cervical spine CT scan. This will be a pilot efficacy trial to compare treatment of odontoid fractures with PTH analog + hard collar immobilization in comparison to historical treatment with hard collar immobilization alone.

Treatment subjects:

Patients will be identified and recruited when presenting with acute fracture to our medical center. Under routine care at our center, all cervical spine fractures are evaluated, either in person or via tele-consult for remotes sites, by a fellowship trained Orthopedic or Neurosurgical Spine surgeon at the time of injury/hospitalization. If deemed amenable to non-operative treatment, that patient is then referred to the spine fracture clinic for serial clinical and radiographic follow-up.

The study will be introduced to the patient by a PI-delegated provider from the study team either during hospitalization or at their first visit to the spine fracture clinic – typically within 2 weeks of injury. Informed consent for this study may thus be obtained at one of two locations: (1) A majority (~75%) of these patients are admitted to the hospital; these patients will be introduced to the study by a PI-delegated provider who is key personnel on the study team, and may be consented while in the hospital. (2) Other patients may be identified and recruited from our Orthopedic Spine Fracture clinic, which is the referral repository for all non-operatively managed spine fractures within our health system.

Patients with acute Anderson & D'Alonzo type II dens fractures, +/- C1 ring injury, identified on cervical CT scan, and recommended for non-operative treatment will be recruited for enrollment in the study (see Inclusion/Exclusion Criteria, below). Acuity of the fracture will be determined by radiographic appearance, pain, and mechanism. Type II fractures are defined as described by Grauer et.al as involving the area of the dens between the inferior aspect of the anterior C1 ring and not extending into the superior articular facets of C2.[9]

If a patient consents to participation in the study, baseline labs will be drawn (see Table 1). The study team's endocrinologist will review labs and confirm their eligibility for the study. Lab values obtained during the screening process (see Screening Procedures below) could exclude patients include an elevated PTH or hypercalcemia. Given the medical complexity, there will not be hard cutoff values for the labs (see Inclusion/Exclusion Criteria, below) – but rather eligibility to participate will be left to the clinical judgement of our endocrinology investigator (Dr. Jennifer Kelly or another fellowship-trained endocrinologist in her absence who is key personnel on the study).

Eligible patients will receive standard treatment of 12(+/-1) weeks of rigid hard collar immobilization, as well as an 8-week course of PTH analog during this time. Drug will be initiated as soon after the injury as possible, and at the latest 4 weeks from injury which will allow for completion of 8 weeks of drug administration during the period of hard collar immobilization. Teaching on drug administration will be provided for enrolled patients and their caregiver, if applicable, by designated study personnel prior to drug initiation – either while inpatient, or at the outpatient endocrinology clinic visit. Treatment subjects will otherwise receive the routine care that was provided to historical controls in terms of length of hard collar immobilization spine fracture clinic follow-up and radiographic evaluation. Treatment subjects will be followed with weekly phone calls (see Table 1) by clinical personnel on the study team for the duration of the 8-week treatment.

Study participants will be followed at the spine fracture clinic according to our usual protocol every 4 weeks +/- 1 week (from the date of injury) out to 12 weeks. All patients will fill out VAS Neck and Neck Disability Index (NDI) physical function questionnaires at each clinic visit. Use of narcotic pain medication will be collected at each clinic visit under routine care.

DEXA scans will be obtained for all participants to assess baseline bone density. If a patient has had a DEXA scan for routine care within the 12 months prior to consent, that scan will be used as the baseline test and a separate test for research will not be ordered. If needed, baseline DEXA will need to be completed after consent and by time of the 12 week visit.

All radiographs for treatment subjects will be obtained as part of routine care. These include AP/Lateral at each of the 4 (+/-1) week and 8 (+/-1) week clinic visits, and Flex/Ext at the 12 (+/-1) week clinic visits. Final (12 +/-1 week) flexion/extension radiographs will be evaluated for translational motion at the fracture site measured at the posterior cortex of the dens and evaluated by the following criteria: None, Minimal (<2 mm), Moderate (2-4 mm), Mobile (>4 mm).

A non-contrast cervical spine CT scan at will be obtained for research purposes at UVMMC at the 12 (+/-1) week time point. Final fracture characteristics (angulation, displacement) will be documented based on the 12-week CT scan. Amount of fracture healing will be assessed on CT by a radiologist by the following method[10]: 1 mm coronal and sagittal sections across the fracture will be individually analyzed. The radiologist will reconstruct the CT scan to true orthogonal coronal and sagittal images. Each slice will be analyzed for the width of bridging bone as a percentage of the width of the facture line. The sum total of the widths of bridging bone, divided by the sum total of the fracture widths will be expressed as a percentage of total healing for that patient. This absolute % of bridging bone will be the primary outcome[10]. Fracture characteristics (obliquity, angulation, displacement, comminution) on the injury CT scan will be documented for later post-hoc analysis. Additionally, we will also compare our study group results to the union rates documented in the existing literature.

Control subjects:

Our historical control group will be comprised of patients with type II odontoid fractures (defined above) who were previously treated in our spine fracture clinic. Patients will have been injured within the past ten years, and have completed 12 +/-1 weeks of hard collar immobilization. Potentially eligible historical controls will be identified by database query and chart/radiographs review of patients from the fracture clinic. A request will be made of the UVMMC Data Management Office to identify potential control subjects. Identified potential control patients will be approached as outlined under 'Consent Process', below.

If patients are interested in active study participation by coming in for a study visit (research imaging: *Control cohort A: Active control participants*), written informed consent will be obtained in person at UVMMC by designated research personnel. Consented active control subjects will then complete a CT scan of the cervical spine for comparison to those from our study group. If flexion-extension cervical XR were not obtained 11 or more weeks after initiation of hard collar treatment as part of their routine care, flexion-extension cervical XR will be obtained for the study. Additionally, these control subjects will complete VAS Neck and NDI physical function questionnaires.

Identified potential control subjects who (a) previously had a cervical CT after completion of hard collar treatment under routine care or (b) were offered participation in Control Cohort A but are not interested in active study participation (i.e. do not consent to come in for study visit) will be invited to verbally consent to allow the study team to collect existing information that is available from their treatment for dens fracture in the electronic medical record, as outlined in 'Procedures for subjects in *control cohort B*', below.

For potential control subjects who are deceased at time of identification, the study team will collect existing information that is available from their treatment for dens fracture in the electronic medical record, as outlined in 'Procedures for subjects in *control cohort B*', below.

All research-driven CT scans will be obtained at UVMMC with the proper imaging protocols and resolution.

9. Grauer, J. N., Shafi, B., Hilibrand, A. S., Harrop, J. S., Kwon, B. K., Beiner, J. M., ... & Vaccaro, A. R. (2005). Proposal of a modified, treatment-oriented classification of odontoid fractures. *The Spine Journal*, *5*(2), 123-129.
10. Jones, C. P., Coughlin, M. J., & Shurnas, P. S. (2006). Prospective CT scan evaluation of hindfoot nonunions treated with revision surgery and low-intensity ultrasound stimulation. *Foot & ankle international*, *27*(4), 229-235.

Procedures: Describe all procedures (sequentially) to which human participants will be subjected. Identify all procedures that are considered experimental and/or procedures performed exclusively for research purposes. Describe the types, frequency and duration of tests, study visits, interviews, questionnaires, etc.

Note: A clinical research protocol may involve interventions that are strictly experimental or it may involve some aspect of research (e.g., randomization among standard treatments for collection and analysis of routine clinical data for research purposes). It is important for this section to distinguish between interventions that are experimental and/or carried out for research purposes versus those procedures that are considered standard therapy. In addition, routine procedures performed solely for research purposes (e.g., additional diagnostic/follow-up tests) should be identified.

Procedures for treatment subjects

Table 1. Study procedures for treatment subjects.

Visit Time point	Screening and baseline procedures	**4-week visit** (within 4 weeks of fracture)	**8-week visit** (8 +/-1 weeks after fracture)	**12-week visit** (12 +/-1 weeks after fracture
Informed consent	X*			
Spine Fracture Clinic visit	X (if needed for routine care)	X	X	X
Physical Exam	X	X	X	X
Neck Disability Index		X	X	X
VAS Neck		X	X	X
(Eligibility confirmed by study team after screening labs completed and before study drug administration)				
Endocrinology Clinic visit (only if the patient is not recruited while inpatient)	X*			
Study drug teaching and first dose of Tymlos	X*			
Tymlos self-administration	X* (daily for 8 weeks after drug teaching)			
CMP	X*			
PTH	X*			
Phos	X*			
HbA1c	X*			
AP/Lateral XR	X	X	X	(X if required for routine care)
Flex/Ext XR				X
CT Cervical	X			X*
DEXA	X** (by time of 12-week visit)			
Phone check-in	X* (each week +/- 2 d after first dose for the 8-week treatment period)			

* These procedures are research-driven and deviate from routine care of treatment patients in clinic.

** The DEXA scan is completed for research purposes only if not previously completed within 12 months before consent for routine care purposes.

Spine fracture clinic (and endocrinology visit, for patients not recruited in the inpatient setting) involve medical history under routine care.

Neck Disability Index and VAS Neck physical function are questionnaires given to patients during the clinic visit and prior to medical evaluation. These take less than 10 minutes to fill out, they are validated, and they are standard/routine in many clinic visits. These questionnaires will provide secondary outcome measures.

The study drug (abaloparatide) is an FDA approved medication used to treat osteoporosis. It is a daily subcutaneous injection administered by the patient. This requires patient education.

CMP, PTH, Phos, and HbA1c are laboratory tests performed by venipuncture. Blood work includes complete metabolic profile, phosphorous, parathyroid hormone, and hemoglobin A1c. Many of these patients have osteoporosis at baseline and these tests allow us to screen, quantify, and subsequently manage their osteoporosis. This blood work is standard of care for evaluation and treatment of osteoporosis. *In this study*, CMP, PTH and Phos will be obtained as screening labs (see Screening Procedures, below). HbA1c

levels are meant for baseline data collection as they relate to the ability to heal fractures, and are tested with screening labs to prevent need for additional blood draws for research purposes.

AP/Lateral XR and Flex/Ext XR is a standard set of X-rays of the cervical spine used to evaluate the secondary outcome of translational motion at the fracture.

CT Cervical spine is for research purposes at the 12-week mark only. This will be used to measure fracture union rate (the primary outcome).

The DEXA scan is a low dose x-ray scan used as a screening tool recommended for all women over the age of 65. The radiation is so low (significantly lower than a chest x-ray) that this machine and radiation is not formally regulated in the United States. Many of these patients have osteoporosis at baseline and this test allows us to screen, quantify, and subsequently manage their osteoporosis. *In this study*, DEXA scans will be obtained to evaluate bone health as it relates to the ability to heal a fracture. If a patient's T-score is <= -2.5 at the spine or hip in a DEXA scan obtained for research purposes, the study team will notify the patient of the finding and refer her/him for follow-up care, as appropriate.

Procedures for control cohort A (active control participants)

Table 2. Research procedures for control patients who provide written consent to active study participation (control cohort A).

Item	UVMMC	Via Mail
Informed consent	X	
Neck Disability Index	X	
VAS Neck	X	
Cervical CT Scan	X	
Flexion-extension cervical x-ray	X**	
Compensation		X*

* After completion of CT scan
** The XR is only obtained for research purposes if a flexion-extension cervical x-ray was not obtained 11 or more weeks after initiation of hard collar treatment as part of their routine care.

Procedures for control cohort B (review-only control participants)

Control cohort B includes subjects who
(a) Previously had a cervical CT scan obtained after completion of their hard collar treatment under routine care; or
(b) do not provide written consent to active study participation but provide verbal consent to allow the study team to collect existing information that is available from their treatment in the electronic medical record; or
(b) are deceased and are not available for informed consent

For these control participants, the study team will collect information that is available in the electronic medical record to support analyses of available outcomes. This information includes demographic information, fracture characteristics and applicable radiographs obtained during their routine care for neck fracture.

Describe required screening procedures performed before enrollment and while on study.

Screening procedures for treatment subjects before enrollment:

At the time of spine surgical consultation, CT scans obtained for routine care will be evaluated and those patients whose fracture types meet the inclusion criteria will be approached to consider participation in the study. After consent is obtained, but prior to enrollment, patients will be screened for eligibility based on their medical history, as well as laboratory values. Laboratory values obtained for eligibility screening will include a Comprehensive Metabolic Panel, PTH and Phos. Based on medical history, Ca, PTH, and Phos levels an endocrinologist on the study team will confirm eligibility for the study prior to enrollment.

Screening procedures for treatment subjects while on study:

Cervical spine x-rays will be obtained at each clinic visit as per our routine non-operative management. These will be reviewed as outlined in Withdrawal Procedures, below.

For research involving survey, questionnaires, etc.: Describe the setting and the mode of administering the instrument and the provisions for maintaining privacy and confidentiality. Include the duration, intervals of administration, and overall length of participation.

[ ] **Not applicable**

Two questionnaires (VAS Neck and Neck Disability Index (NDI) physical function questionnaires) will be administered 3 times for each treatment subject (at each clinic visit: 4 weeks, 8 weeks, and 12 weeks), and once for each control subject. Together the two questionnaires can be completed in under 10 minutes.

For treatment subjects, the questionnaires are administered as part of routine care at these time points, as they are for other patients with dens fractures. The two questionnaires are integrated into our standard practice for all spine patients at clinic. The questionnaires are administered by medical staff in clinic prior to evaluation by the physician. They are completed privately by the patient and inserted into the patient's electronic health record after the visit.

For historical comparison subjects, the questionnaires will be administered by designated study personnel in person at UVMMC. The questionnaires will be completed by the patient after written informed consent is obtained.

TYPES OF PROCEDURES (Please do not use the "other" option unless the procedure is not listed.)
Check all that apply.

X	Survey (mail, telephone, in-person, on-line)	X	Blood drawing:	Vol.		Over days, weeks?	Blood will be drawn for eligibility screening, and HbA1c levels in treatment subjects only
X	Medical exams/history					Type & Amt.	See the tests listed for treatment subjects in Table 1, above.
	Deception ***see below**		Surgery				Collection of Urine and/or Feces
X	Observation	X	Drug Administration				HIV Testing
	Photographs		Device Use				Ultrasound (e.g. echocardiogram)
	Audio Recording		Exercise			X	Imaging (e.g. CT scan, DEXA, mammogram, PET scans, SPECT)
	Video Recording		Diet				Use of Radiation treatment
	Interviews in person or by phone		Pathology Specimens (retrospective)				Use of Radioactive substances (e.g. radiolabeled antibodies, drugs or contrasts)
	Focus Groups		Genetic Materials (DNA)*				MRI (for treatment studies)
X	Review of prospective data	X	Questionnaires				MRI (not for treatment studies)
X	Review of retrospective data	X	Diaries				Tissue (obtained for clinical purposes)
	Recording of Identifiable Data		Pregnancy Tests				Tissue (obtained solely for research)
	Electrocardiograms						
	Sensitive Data (criminal or sexual conduct, drug or alcohol conduct or use)			(specify):			

***If genetic information is being collected, GINA language must be added to the consent form.**
*Deception typically involves withholding information from the potential subject and would require an alteration to the consent process.

Statistical Considerations: Delineate the precise outcomes to be measured and analyzed. Describe how these results will be measured and statistically analyzed. Delineate methods used to estimate the required number of subjects. Describe power calculations if the study involves comparisons. Perform this analysis on each of the primary and secondary objectives, if possible.

Primary outcome will be % bridging bone on CT scan at 12 weeks as described previously based on 1 mm sagittal and coronal cuts. The study radiologist evaluating the primary outcome will be blinded to patient group (treatment vs. historical control). Secondary outcomes will include VAS Neck and NDI scores, and motion on flexion/extension radiographs.

Assuming 60% nonunion rate in our historical control group and 20% in our study group, with alpha = 0.05 and 80% power, we would need to enroll 44 patients in a randomized trial (22 control, 22 study patients) to show a statistical difference. This study is intended as an initial pilot study to suggest efficacy, and further inform a future randomized controlled trial. We see 15-20 new type II dens fractures treated non-operatively per year in our fracture clinic, and estimate the initial pilot of 10 treatment patients + 12 control subjects can be completed within 2 years.

Data analysis will be based on multi-variate regression using ANOVA, with $p<0.05$ recognized as a significant difference. Plan is for as treated analysis; if there are patients who receive only partial course of study drug for any reason, they will be evaluated descriptively as a separate group. Additionally, we will also compare our study group results to the union rates documented in the existing literature.

Risks/Benefits: Describe any potential or known risks. This includes physical, psychological, social, legal or other risks. Estimate the probability that given risk may occur, its severity and potential reversibility. If the study involves a placebo or washout period, the risks related to these must be addressed in both the protocol and consent. Describe the planned procedures for protecting against or minimizing potential risks and assess their likely effectiveness. Where appropriate, discuss plans for ensuring necessary medical or professional intervention in the event of adverse effects to the subjects. Discuss the potential benefits of the research to the subjects and others. Discuss why the risks to the subjects are reasonable in relation to the anticipated benefits to subjects and others. Discuss the importance of the knowledge gained or to be gained as a result of the proposed research and why the risks are reasonable in relation to the knowledge that reasonably may result. If there are no benefits state so.

The study drug has a relatively benign risk profile. Risks of the medication are shown below:

Orthostatic Hypotension

Orthostatic hypotension may occur with TYMLOS (abaloparatide), typically within 4 hours of injection. Associated symptoms may include dizziness, palpitations, tachycardia or nausea, and may resolve by having the patient lie down. For the first several doses, TYMLOS (abaloparatide) should be administered where the patient can sit or lie down if necessary

Hypercalcemia

TYMLOS (abaloparatide) may cause hypercalcemia. TYMLOS (abaloparatide) is not recommended in patients with preexisting hypercalcemia or in patients who have an underlying hypercalcemic disorder, such as primary hyperparathyroidism, because of the possibility of exacerbating hypercalcemia. Patients will be screened by our endocrinologist who will review baseline calcium levels and underlying hypercalcemic disorders. Patients with persistent hypercalcemia or hypercalcemia refractory to treatment, will be evaluated by our endocrinologist, and if appropriate, these patients will be excluded at the discretion of an endocrinologist on the study team.

Hypercalciuria and Urolithiasis

TYMLOS may cause hypercalciuria. It is unknown whether TYMLOS may exacerbate urolithiasis in patients with active or a history of urolithiasis. If active urolithiasis or pre-existing hypercalciuria is suspected, measurement of urinary calcium excretion should be considered. Patients will be screened by our endocrinologist who will review urine and serum calcium levels and active or recurrent urolithiasis. Patients with hypercalciuria or urolithiasis, if appropriate, will be excluded at the discretion of the endocrinologist.

Risk of Osteosarcoma

Abaloparatide caused a dose-dependent increase in the incidence of osteosarcoma in male and female rats after subcutaneous administration at exposures 4 to 28 times the human exposure at the clinical dose of 80 mcg. It is unknown whether TYMLOS will cause osteosarcoma in humans. The use of TYMLOS is not recommended in patients at increased risk of osteosarcoma including those with Paget's disease of bone or unexplained elevations of alkaline phosphatase, open epiphyses, bone metastases or skeletal malignancies, hereditary disorders predisposing to osteosarcoma, or prior external beam or implant radiation therapy involving the skeleton. Cumulative use of TYMLOS and parathyroid hormone analogs (e.g., teriparatide) for more than 2 years during a patient's lifetime is not recommended. In our study, we are excluding anyone who has had any exposure to these anabolic medications in the past. Our duration of treatment is only 8 weeks.

Screening for the above risks in treatment subjects will be performed via weekly phone calls and monthly clinic visits (Table 1) for the 12-week study period. The historical cohorts do not have the above risks as they are not being treated with the study medication. Other potential risks to both the treatment and historical comparison groups are listed below:

CT-Cervical Spine

Risk to our treatment cohort and control cohort A includes the radiation exposure of the additional imaging, which is relatively minimal. A CT scan of the cervical spine is approximately 2.8mSv shown in the literature and confirmed at our institution, the equivalent of approximately 1 year of background radiation from the sun[11]. Additionally, data suggest that beyond ~age 40 there is minimal detriment to small increases in radiation exposure. Particularly given the age distribution of our study population, this small amount of additional radiation is of minimal to no additional risk[12].

Risk of breach of confidentiality

There is a risk of loss of confidentiality. To minimize this risk, identifiable paper records (e.g. written informed consent forms) will be kept in locked offices and identifiable electronic data will be maintained in the secure LCOM shared drive and database (see the

study's Research Data Management and Security Plan). Access to identifiable paper and electronic study records will be restricted to research personnel. In addition, identifiable information will not be disclosed outside of the study site, except when medically necessary (i.e. if a medical condition is incidentally discovered during the course of the study, and the participant gives permission to disclose that information to the her/his primary care physician). Radiographic images will be retained in participants' electronic health records.

Potential Benefit

No treatments will be withheld as part of participation in this study. This study is being carried out because it is unknown whether the study medication will make dens fractures more likely to heal or not. By the nature of this injury, many if not all of these patients are expected to have osteoporosis. The DEXA scan may be of benefit if it results in early diagnosis and management of previously undiagnosed osteoporosis. In treatment subjects, the study medication TYMLOS (abaloparatide) could provide early treatment of osteoporosis.

While we do not know whether individual participants will benefit directly from their participation in this study, there may be indirect benefit if the knowledge gained allows the medical community to expand its treatment for fractures in the elderly and minimize the use of high-risk surgery in older adults with dens fractures in future.

The risks are relatively benign and therefore the potential benefits appear to outweigh the risks.

11. Cohnen, M., Poll, L. W., Puettmann, C., Ewen, K., Saleh, A., & Mödder, U. (2003). Effective doses in standard protocols for multi-slice CT scanning. *European radiology*, *13*(5), 1148-1153.
12. Brenner, D. J., & Hall, E. J. (2007). Computed tomography—an increasing source of radiation exposure. *New England Journal of Medicine*, *357*(22), 2277-2284.

Therapeutic Alternatives: List the therapeutic alternatives that are reasonably available that may be of benefit to the potential subject and include in the consent form as well.

☐ **Not Applicable**

The therapeutic alternative to our study population is the treatment given to our historical controls. This treatment is with a hard collar alone (without the use of abaloparatide).

Data Safety and Monitoring: The specific design of a Data and Safety Monitoring Plan (DSMP) for a protocol may vary extensively depending on the potential risks, size, and complexity of the research study. For a minimal risk study, a DSMP could be as simple as a description of the Principal Investigator's plan for monitoring the data and performance of safety reviews or it could be as complex as the initiation of an external, independent Data Safety and Monitoring Board (DSMB). The UVM/UVM Medical Center process for review of adverse events should be included in the DSMP.

There is a risk of loss of confidentiality. The study team's procedures to mitigate this risk and promote both physical security and confidentiality of subjects' data and records are outlined in the attached Research Data Management and Safety Plan and described under 'Risks/Benefits', above.

This study will follow the UVM IRB's policies and procedures for reportable new information. Unanticipated problems will be evaluated by the PI on a rolling basis and reported per IRB requirements.

The study does not have an external, independent Data Safety and Monitoring Board. A Data Safety Officer will be delegated responsibility for independent data validation (verification against source documentation). Data validation will be performed once annually.

Define criteria to be used for decision making regarding continuation, modification, or termination of the entire study (not individual participation) (i.e. "stopping rules).

Decision-making for the entire study: Modification or termination would be considered if there are repeated and severe adverse events attributed to the study drug. Based on study profile, the team believes this would be unlikely.

At both the participant and study levels, decisions regarding continuation/modification/termination will be at the discretion of the PI.

What will be the frequency of the review? Please note that the frequency of reviews should be commensurate with the risk of the study. At a minimum, a review of the data should be conducted annually at time of continuing review. **Forward copies of the data and safety monitoring reports to the 1) IRB, 2) CRC (if applicable), and/or 3) UVMCC (if applicable).**

- [ ] Monthly
- [ ] Quarterly
- [ ] Bi-annually
- [X] Annually
- [ ] Other (e.g. by dosing level, no. of subjects enrolled):

Will the sponsor be conducting data monitoring visits for this study?

- [ ] Yes
- [ ] No
- [X] NA

If yes, how often?

Adverse Event, Unanticipated Problem (UAP), Reportable New Information (RNI): Describe how events and UAPs will be evaluated and reported to the IRB. All protocols should specify that, in the absence of more stringent reporting requirements, the guidelines established in the "Adverse Event and Unanticipated Problems Reporting Policy" will be followed. The UVM/UVM Medical Center process for review of adverse events and UAPs to subjects or others should be included in the DSMP.

Regular monitoring for adverse events will be performed via weekly phone calls and monthly clinic visits (Table 1) throughout the 12-week study period.

The guidelines established in the UVM IRB's "Adverse Event and Unanticipated Problems Reporting Policy" will be followed. Adverse events include any unfavorable medical occurrence/sign/symptom that a patient experiences while participating in the study, whether these events are considered related to the study medication or not. Pre-existing conditions that do not worsen during the study will not be considered adverse events.

All adverse events and serious adverse events will be classified as expected vs unexpected; and classified as probably related to the study medication or not.

The following will be classified as serious adverse events based on the PI's judgement and following the UVM IRB's guidelines: any untoward medical occurrence that results in death or is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, leads to persistent or significant disability and/or incapacity, causes a congenital anomaly and/or birth defect, or requires medical intervention to prevent any of these outcomes.

Withdrawal Procedures: Define the precise criteria for withdrawing subjects from the study. Include a description of study requirements for when a subject withdraws him or herself from the study (if applicable).

Under routine care, patients with dens fractures are monitored for any fracture displacement using x-rays or neurologic changes that require a change in treatment plan. Study participants will be monitored in the same way. For treatment subjects: if the fracture clinic physician Dr. Flimlin has any concerns for abnormal fracture displacement or new neurologic deficit, the PI (or another fellowship-trained orthopaedic or neurologic spine surgeon on the study team as delegated by the PI) will review all radiographic evidence of fracture displacement or neurologic deficit. Based on fracture displacement and neurologic changes, the patient may require a change in their treatment plan. Study patients are treated no differently from non-study patients in this regard. If there is a significant change in their treatment plan (e.g. surgery), these patients will be withdrawn from the study at the discretion of the PI.

All study participants may voluntarily withdraw themselves from the study at any time. If a participant decides to withdraw, the study will continue to use the information already collected for the study before withdrawal. This is noted in the informed consent forms for both control and treatment subjects.

If a patient were withdrawn from the study for any reason, the standard of care treatment for their fracture would resume.

Sources of Materials: Identify sources of research material obtained from individually identifiable human subjects in the form of specimens, records or data. Indicate whether the material or data will be obtained specifically for research purposes or whether use will be made of existing specimens, records or data.

Sources of research information will be provided in the electronic health records (including imaging) and study questionnaires. This information will be used for eligibility screening, safety monitoring, primary outcome (CT scans) and secondary outcome (radiographs, VAS and NDI) measures. Material will be derived from both existing sources in the electronic health record and research-driven procedures. Together these materials include:

For treatment subjects
- Lab results and office notes
- Office notes from clinical exams and consultations, including VAS Neck and NDI measures
- Radiographs and CT scans
- Drug diary

For historical comparison subjects (Control cohort A: active control participants)
- Lab results and office notes
- Study questionnaires (VAS Neck and NDI)
- Radiographs and CT scans

For historical comparison subjects (Control cohort B: review-only control participants)
- Lab results and office notes (incl. eligibility criteria, demographic information, and dens fracture characteristics)
- Radiographs
- VAS Neck and NDI measures, if they were recorded at routine care visit in the past

DRUG INFORMATION

Investigators are encouraged to consult the UVM Medical Center Investigational Pharmacy Drug Service (847-4863) prior to finalizing study drug/substance procedures.

Drug (s) ☐ **Not applicable**

Drug name – generic followed by brand name and common abbreviations. Availability – Source and pharmacology; vial or product sizes and supplier. If a placebo will be used, identify its contents and source.

Abaloparatide (TYMLOS)

Preparation: Reconstitution instructions; preparation of a sterile product, compounded dosage form; mixing guidelines, including fluid and volume required. Identify who will prepare.

TYMLOS injection is supplied as a pre-assembled single-patient-use disposable pen (NDC70539-001-01) packaged in a cardboard carton (NDC 70539-001-02) with the Instructions for Use and Medication Guide. Each disposable pen embodies a glass cartridge that contains 3120 mcg of abaloparatide in 1.56 mL (2000 mcg/mL) of sterilized, clear, colorless fluid. Each pen provides a 30-day supply for once daily injection of 80 mcg abaloparatide in 40 mcL. Sterile needles will be provided by the study.

Storage and stability – for both intact and mixed products.

Before first use, store TYMLOS in a refrigerator between 2°C to 8°C (36°F to 46°F).
After first use, store for up to 30 days at 20°C to 25°C (68°F to 77°F).
Do not freeze or subject to heat.
The medication will be stored at UVMMC in a refrigerator between 2°C to 8°C (36°F to 46°F) prior to use. It will be dispensed by the pharmacy for all participants for whom eligibility confirmation and consent are obtained at the inpatient setting. For subjects who are not consented and/or for confirmed as eligible until they are treated in the outpatient setting, the study drug will be picked up by a member of the research team and transported to the outpatient clinic for the time of drug teaching.

Medication will be dispensed on Monday through Friday during working pharmacy hours. Participants will receive both pens at time of drug teaching and first dose administration. Participants will be monitored for approximately 15-20 minutes after their first injection. Teaching will be performed by designated nurses from the study team in either the inpatient setting or endocrinology clinic, for patients and their caregivers, if applicable.

Administration – Describe acceptable routes and methods of administration and any associated risks of administration.

Recommended dose is 80 mcg subcutaneously once daily. There is a small risk of minimal bleeding. Advised to administer initially where the patient can sit or lie down in case symptoms of orthostatic hypotension occur. Administration of the first dose will be performed in person with a designated nurse from the study team.

Toxicity – Accurate but concise listings of major toxicities. Rare toxicities, which may be severe, should be included by indicated incidence. Also adverse interactions with other drugs used in the protocol regimen as well as specific foods should be noted. Address significant drug or drug/food interactions in the consent form as well. List all with above details.

Orthostatic Hypotension

Orthostatic hypotension may occur with TYMLOS (abaloparatide), typically within 4 hours of injection. Associated symptoms may include dizziness, palpitations, tachycardia or nausea, and may resolve by having the patient lie down. For the first several doses, TYMLOS (abaloparatide) should be administered where the patient can sit or lie down if necessary

Hypercalcemia

TYMLOS (abaloparatide) may cause hypercalcemia. TYMLOS (abaloparatide) is not recommended in patients with preexisting hypercalcemia or in patients who have an underlying hypercalcemic disorder, such as primary hyperparathyroidism, because of the possibility of exacerbating hypercalcemia. Patients will be screened by our endocrinologist who will review calcium levels and underlying hypercalcemic disorders. Patients with persistent hypercalcemia or hypercalcemia refractory to treatment, will be identified by our endocrinologist, and if appropriate, these patients will be excluded at the discretion of the endocrinologist.

Hypercalciuria and Urolithiasis

TYMLOS may cause hypercalciuria. It is unknown whether TYMLOS may exacerbate urolithiasis in patients with active or a history of urolithiasis. If active urolithiasis or pre-existing hypercalciuria is suspected, measurement of urinary calcium excretion should be considered. Patients will be screened by our endocrinologist who will review urine and serum calcium levels and active or recurrent urolithiasis. Patients with hypercalciuria or urolithiasis, if appropriate, will be excluded at the discretion of the endocrinologist.

Risk of Osteosarcoma

Abaloparatide caused a dose-dependent increase in the incidence of osteosarcoma in male and female rats after subcutaneous administration at exposures 4 to 28 times the human exposure at the clinical dose of 80 mcg. It is unknown whether TYMLOS will cause osteosarcoma in humans. The use of TYMLOS is not recommended in patients at increased risk of osteosarcoma including those with Paget's disease of bone or unexplained elevations of alkaline phosphatase, open epiphyses, bone metastases or skeletal malignancies, hereditary disorders predisposing to osteosarcoma, or prior external beam or implant radiation therapy involving the skeleton. Cumulative use of TYMLOS and parathyroid hormone analogs (e.g., teriparatide) for more than 2 years during a patient's lifetime is not recommended. In our study, we are excluding anyone who has had any exposure to these anabolic medications in the past. Our duration of treatment is only 8 weeks (instead of the 2-year recommendation by the company) which further minimizes this risk.

Toxicity

In toxicity studies in rats and monkeys of up to 26-week and 39-week duration, respectively, findings included vasodilation, increases in serum calcium, decreases in serum phosphorus, and soft tissue mineralization at doses greater than or equal to 10 mcg/kg/day. The 10 mcg/kg/day dose resulted in systemic exposures to abaloparatide in rats and monkeys that were 2 and 3 times, respectively, the exposure in humans at daily subcutaneous doses of 80 mcg.

Is it FDA approved: (include FDA IND Number)

1. in the dosage form specified? If no, provide justification for proposed use and source of the study drug in that form.

   Yes PIND 146326, NDA 208743

2. for the route of administration specified? If no, provide justification for route and describe the method to accomplish.

   Yes

3. for the intended action?

   No. However, the proposal involves use as an experimental treatment of a fracture that is most common in elderly patients with osteoporosis, and the study drug is approved for the treatment of individuals with osteoporosis who are at high risk for these fractures.

SUBJECT CHARACTERISTICS, IDENTIFICATION AND RECRUITMENT

Subject Selection: Provide rationale for subject selection in terms of the scientific objectives and proposed study design.

The study population includes patients greater than or equal to the age of 50. This is the population that sustains dens fractures most frequently.

Vulnerable Populations: Explain the rationale for involvement of subjects (e.g., cognitively impaired, Non-English speaking, prisoners, students). Discuss what procedures or practices will be used in the protocol to minimize their susceptibility to undue influences and unnecessary risk (physical, psychological, etc.).

X	**Not applicable**

Inclusion/Exclusion Criteria: Eligibility and ineligibility criteria should be specific. Describe how eligibility will be determined and by whom. Changes to the eligibility criteria at a later phase of the research have the potential to invalidate the research.

Treatment Subjects

Inclusion Criteria (all must be yes)

1. Age 50 years or older at time of consent
2. Anderson and D'Alonzo type II dens fracture identified on cervical spine CT, with or without a C1 ring injury. Type II dens fractures are defined as involving the area of the dens between the inferior aspect of the anterior C1 ring and not extending into the superior articular facets of C2.
3. Fracture is deemed amenable to non-operative treatment by treating fellowship trained spine surgeon
4. Fracture occurred within the 3 weeks before consent
5. Report of >=12 months of amenorrhea within the last year if the patient is female

Exclusion Criteria (all must be no)

6. Personal history of radiation therapy to the skeleton
7. Personal history of osteosarcoma
8. Personal history of Paget's disease
9. Personal history of bone metastases or skeletal malignancy
10. Hereditary disorders predisposing to osteosarcoma
11. Prior teriparatide or abaloperatide use
12. Use of denosumab within the past year
13. Psychological impairment that precludes following hard collar immobilization recommendations
14. Ineligible based on history of active or recurrent kidney stones, CMP, PTH, Phos results to be determined on a case-by-case basis by an endocrinologist on the study team

Historical Comparison Subjects

Inclusion Criteria (all must be yes)

1. Age 50 years or older at time of fracture
2. Anderson and D'Alonzo type II dens fracture identified on cervical spine CT, with or without a C1 ring injury. Type II dens fractures are defined as involving the area of the dens between the inferior aspect of the anterior C1 ring and not extending into the superior articular facets of C2.
3. Fracture injury occurred within 10 years before consent
4. The patient completed 12 (+/- 1) weeks of hard collar immobilization

Exclusion Criteria (all must be no)

5. Any history of prior teriparatide or abaloparatide use
6. Use of denosumab in the past year

Inclusion of Minorities and Women: Describe efforts to include minorities and women. If either minorities or women are excluded, include a justification for the exclusion.

Women will be included in the study whenever the eligibility criteria are met. Every effort will be made to recruit minorities. Recruitment efforts will not differ by sex or by ethnicity.

Inclusion of Children: Describe efforts to include children. Inclusion is required unless a clear and compelling rationale shows that inclusion is inappropriate with respect to the health of the subjects or that inclusion is inappropriate for the purpose of the study. If children are included, the description of the plan should include a rationale for selecting or excluding a specific age range of children. When included, the plan must also describe the expertise of the investigative team in working with children, the appropriateness of the available facilities to accommodate children, and the inclusion of a sufficient number of children to contribute to a meaningful analysis relative to the purpose of the study. Provide target accrual for this population. Identify whether children are wards of the state. **If children are excluded** then provide appropriate justification.

The fracture of interest occurs very rarely in minor subjects, and the safety and effectiveness of the study drug has not been established in pediatric patients. Children will not be included in this study.

For protocols including the use of an investigational drug, indicate whether women of childbearing potential have been included and, if not, include appropriate justification.

The study drug is not indicated for use in females of reproductive potential and the safety of the study drug in pregnant women is unknown. We are therefore limiting recruitment to that of older adults (>=age 50). Women of childbearing potential will not be included in this study.

If HIV testing is included specifically for research purposes explain how the test results will be protected against unauthorized disclosure. Include if the subjects are to be informed of the test results. If yes, include the process and provision for counseling. If no, a rationale for not informing the subjects should be included.

X **Not applicable**

Will the SONA psychology Pool be utilized? *Include documentation indicating permission to use this recruiting tool* Yes [ ] No [X]

FINANCIAL CONSIDERATIONS

Describe all potential research related expenses to subjects:

Any additional study process or test that is beyond the routine medical costs for non-operative management of dens fracture will be covered by the study; such research-driven procedures are indicated in Tables 1 and 2 above for each of the treatment and control groups, respectively. No additional cost will be charged to the treatment subjects for participating in the study, other than travel to clinic if needed.

Compensation for participation: Describe all plans to pay subjects, either in cash, a gift or gift certificate. Please note that all payments must be prorated throughout the life of the study. The IRB will not approve a study where there is only a lump sum payment at the end of the study because this can be considered coercive. The amount of payment must be justified. Clarify if subjects will be reimbursed for travel or other expenses.

[ ] **Not applicable**

The active control subjects (Control cohort A) will be compensated $50 via mail after research clinic visit, in compensation for their travel and time in returning to clinic for research procedures.

Collaborating Institutions

Will this research be conducted in collaboration with other sites at other locations? Yes [ ] No [X]

If so, complete the following for all collaborating institutions:

Institution Name	Describe Involvement	Is there an IRB? If yes, attach approval or explanation	Are other permissions required? If yes, attach approval or explanation

INFORMED CONSENT

a. Type of Consent

i. Are you obtaining Written Consent? **X** Yes ☐ No

If yes, will there be more than one consent document? **X** Yes ☐ No

If yes, how many consent documents and for what populations.

Two written informed consent forms will be used; one for the treatment subjects and one for the historical comparison subjects. Two consent forms will be used because the study procedures and associated risks for the treatment subjects are different from those for the comparison subjects.

ii. Are you requesting a Waiver of Informed Consent? ☐ Yes **X** No

This request means that you will not be obtaining verbal nor written consent. **If yes**, complete the form Request for a Waiver of Informed Consent/Authorization/Documentation in UVMClick.

iii. Are you requesting an Alteration of Informed Consent Procedures? ☐ Yes X No

This is a request to alter an individual's informed consent or elements of informed consent. Deception in research would be one example when consent would be altered. See Policies and Procedures Manual for more information about when a subject's consent may be altered. **If yes**, complete the smart form Request for a Waiver of Informed Consent/ Authorization/ Documentation in UVMClick.

iv. Are you requesting a Waiver of Documentation of Informed Consent? X (see Informed Consent: b(ii), below for verbally-consented participants in control cohort B) Yes ☐ No

This request means you are obtaining verbal or implied consent without obtaining the subject's signature on a consent form. See manual for the criteria required to obtain this type of waiver.

If yes, complete the form Request for a Waiver of Informed Consent/Authorization/Documentation in UVMClick.

v. Do you intend to obtain consent from a legally authorized representative? ☐ Yes X No

If yes, describe the process.

vi. Are you requesting a short form consent process for non-English speaking subjects? ☐ Yes X No

If yes, please describe. Guidance available in the Policies and Procedures Manual.

b. Consent Process

i. Once a prospective subject is identified, who initiates the informed consent discussion and answers questions presented by the subject or the subject's family?

Designated key personnel of the study will be able to initiate the informed consent discussion and answer questions presented by the subject of the subject's family.

ii. Where (in what setting) is the informed consent process initiated? How much time is the subject given to decide?

For the treatment subjects, ideally the informed consent process will be initiated in the hospital setting within a

day or two after the diagnosis. If the patient is diagnosed at an outside facility and presents to the outpatient spine clinic for follow up, the informed consent process would be initiated there.

For potential control subjects who are living at time of identification and have not previously had a cervical CT under routine care after completion of hard collar treatment: the informed consent process will be initiated either in person or via letter or email from Dr. Flimlin. Designated research personnel will follow-up in person or by phone within two weeks to inquire about interest in study participation. The same, approved recruitment phone script will be used whether it is in person or by phone.

- For participants interested in active study participation (*control cohort A*), written informed consent will be obtained in person at UVMMC in a private room, prior to study imaging or administration of the study questionnaires.
- For eligible control subjects who indicate at time of recruitment phone call that they are not interested in active study participation, the patient will be invited to verbally consent to participation in *control cohort B*. A verbal consent script has been developed for this purpose.

Potential control subjects who are living at time of identification and have previously had a cervical CT under routine care after completion of hard collar treatment will be approached using the approved verbal consent script described above. The verbal consent script offers the opportunity for (passive) participation *in control cohort B* and introduces the researcher as a member of Dr. Flimlin's research team.

In all cases, subjects will be given as much time as they need to discuss the study with others and make their decision. However, treatment patients and comparison subjects will need to be enrolled within 3 weeks of fracture injury and 10 years of fracture injury, respectively, to be eligible for study participation (see Inclusion and Exclusion Criteria, above).

iii. Is the principal investigator present for the initial and subsequent informed consent discussions with the subject?

Either the PI or other designated key study personnel will be present for the initial and subsequent consent discussions with the subject.

iv. What other method of documentation is used to record the informed consent process, in addition to the executed consent form? See an example of documentation of the informed consent **process** under consent templates on our forms page.

Written informed consent processes will be documented using an Informed Consent Process Documentation form. This form is based on the standard IRB template and will be filed together with the informed consent form in the study folder for each consented subject.

Verbal consent processes will be documented using an Informed Consent Process Documentation form. This form will be maintained together with a record of the verbal consent script used for that subject.

Information Withheld From Subjects: Will any information about the research purpose and design be withheld from potential or participating subjects? If so, explain and justify the non-disclosure and describe plans for post-study debriefing.

[X] **Not applicable**

Research Data Management Plan: The Research Data Management and Security Plan form must be completed. The form, along with guidance, can be found in our forms library and must be submitted with your initial application.

University of Vermont Consent to Participate in Research

Title of Research Project:	**Effect of PTH analog on union rates of Type II odontoid fractures in older adults**
Lead Investigator:	**David Lunardini, MD**
Sites Where Research is Being Conducted:	**University of Vermont Medical Center**
Sponsor:	**University of Vermont Larner College of Medicine**

Introduction

You are being invited to take part in this research study because you are over 50 years old and broke a bone in your neck, called the dens, for which you are starting a non-operative 12 week treatment course of hard collar immobilization. This study is being conducted by the University of Vermont at the UVM Medical Center.

Your participation in this research study is optional. We encourage you to ask questions and take the opportunity to discuss the study with anybody you think can help you make this decision.

Key Information to Help You Decide Whether or Not This Study Is Right for You

Here's some background – dens fractures are the most common spine fracture in the elderly. If the fracture does not heal, it could lead to people having pain and disability. Most commonly, patients who don't heal experience neck pain. Less commonly, patients may develop weakness in the arms and legs or develop difficulty walking. Even with treatment in a rigid neck collar, on average the fracture only heals half of the time, with some reports finding that almost 9 out of 10 people do not heal the fracture. If this fracture does not heal, sometimes surgery is required. Surgery for this fracture carries many potential complications such as wound infection, bleeding, difficulty swallowing, and spinal cord injury.

This is a research study to find out if a medication called abaloparatide (Tymlos) can be used to improve healing of dens fractures. You have the option to not participate in this study. If you choose to participate in this study, you will take Tymlos, a daily injection medication that is FDA-approved in the treatment of osteoporosis (thin bones) in postmenopausal women. It is commonly used to treat osteoporosis in men but is not FDA-approved for men specifically, nor is it currently FDA approved as a treatment for dens fractures.

Whether or not you participate in this study, your usual care will include 12 weeks of hard collar immobilization with routine clinic visits every 4 weeks for a physical exam, questionnaire administration, and x-ray. If you would like to participate, you will have blood tests performed and you may be asked to have a bone density (DEXA) scan. If you are a candidate to proceed, you will also be given Tymlos, the study drug, for 8 weeks, and after completing a total of 12 weeks in the hard collar, you will get a final CT scan of your neck to measure if the fracture has healed.

We are testing two groups – people who take the study drug and people who did not. You are

being consented to be in the group of people who take the study drug.

Tymlos has some risks. These include a temporary drop in blood pressure, making you feel lightheaded, dizzy, or faint. Other common reactions include dizziness, nausea, headache, palpitations, fatigue, upper abdominal pain and vertigo. Tymlos may also cause a change in your blood calcium levels. It may cause high levels of calcium in your urine, possibly resulting in kidney stones. There is a risk of developing an immune resistance to the medication, which can lead to allergic reactions such as rash, swelling, or anaphylaxis. This is why your blood would be tested and reviewed by an endocrinologist before you begin taking the study medication. Since Tymlos is administered by a subcutaneous injection (an injection under the skin) into the periumbilical region of the abdomen (around the belly button), you may experience redness or swelling at the injection site. There is also a very small risk of developing bone cancer with prolonged use (greater than 2 years) of Tymlos. Normally, this medication is prescribed for less than two years because of that risk. If you decide to participate in this study, you will be asked to use this medication for 8 weeks. There is also a risk of radiation exposure with another CT scan of your neck. This amount of radiation is small and similar to the amount of background radiation you are exposed to during one year of your regular life from the light from the sun.

We would prefer to avoid surgery when possible. Many people with this fracture also have osteoporosis, and may benefit from Tymlos, the study drug. There have been other studies in humans that show this medication is safe and helps broken bones heal in other parts of the body. We are doing this study to determine if this medication helps dens fractures heal as well.

The information above is only a brief summary of the study. If you are interested in learning more, it is important to read the following pages for additional detailed information about the study. If you decide to take part in the research, you will be asked to provide written consent at the end of this document.

Why Is This Research Study Being Conducted?

Dens fractures are the most common spine fractures in elderly people. Almost 9 out of 10 people over the age of 50 with these fractures do not end up healing because the bone does not grow back together. If this bone does not heal, people can have pain and disability, and sometimes these people end up needing surgery to help the bone heal, which carries risks. We are investigating another, non-operative way to help the bone heal with medication. Abaloparatide (Tymlos), which is used in people with osteoporosis (thin bones), helps heal other broken bones in the body. We are conducting this research study to determine if this medication may also help heal dens fractures. Abaloparatide works by mimicking a normal body hormone (parathyroid hormone or PTH). This hormone stimulates cells to increase bone formation, which may be helpful for healing your fracture.

What Is Involved In The Study?

Our study compares the standard treatment for dens fractures with the standard treatment for dens fractures plus Tymlos. Tymlos has NOT been approved by the Food and Drug Administration (FDA) to treat dens fractures, but has been approved to treat osteoporosis in post-menopausal women.

Because this injury occurs in people with thin bones (osteoporosis), we get blood work at the beginning of the study and a bone density (DEXA) scan to evaluate your overall bone health. Most people that have a dens fracture also have osteoporosis. You will be notified if you have osteoporosis after your DEXA scan within 2 weeks of your results coming back, and referred for follow-up care, if appropriate.

The standard treatment for dens fracture is wearing a hard neck collar for 12 weeks. Whether or not you choose to participate in this research study, you will be given a hard neck collar right away. If you decide to participate, you will undergo additional testing, described in the next paragraph. Within 4 weeks after your injury, you will start taking self-administered daily Tymlos injections. The first time you take this medication, it will be under medical supervision in a hospital or clinic setting. You will be taught how to administer the medication yourself. You will be taught how to properly dispose of the injection needle once it is used. You will remain in the hard neck collar and take this injection daily at home. Your results will be compared to patients who are treated only with a hard neck collar and no drug.

We have doctor visits at 4-week, 8-week, and 12-week marks after fracture. These appointments will be at the same time as your standard doctor visits. During these doctor visits, we check up on your neck pain, perform a physical exam, administer a questionnaire, and get x-rays of your neck. This is part of routine care for patients with neck fractures. These visits may last approximately one hour each. You will also receive weekly phone calls to check in on your progress. After 12 weeks of hard collar treatment, you will get a CT scan, which is an advanced three-dimensional (3D) x-ray, of your neck to see if your bone has healed.

During the study, you will be asked to keep a Drug Diary, which involves recording and keeping track of every medication and drug you take each day, and what times you take them.

Identifiable private information collected from you during this study may be used for future research studies or shared with other researchers for future research. Identifiable private information may be used for future research of many diseases or conditions. If the investigator distributes your information to other researchers or institutions, your information will be labeled with a research code so that you cannot be identified. No additional consent will be requested for the future research use of your samples or information collected from you during this study.

What Are The Risks and Discomforts Of The Study?

Tymlos has NOT been approved by the Food and Drug Administration (FDA) to treat dens fractures, but has been approved to treat osteoporosis in post-menopausal women. The discomforts of Tymlos injections may include bruising, swelling, and pain at the injection site. Severe reactions are rare, reported to occur in between 4 and 29 out of 1,000 people.

The risks of Tymlos include the possibility of a temporary drop in blood pressure usually within 4 hours of taking the medication, making you feel lightheaded, dizzy, or faint. The first dose will be given to you under close medical supervision, either in the hospital or clinic. For the first few doses, the medication should be given while you are sitting and somewhere you will have the option to lie down if needed. Other common reactions include dizziness, nausea, headache, palpitations, fatigue, upper abdominal pain and vertigo. Tymlos may also cause a change in your blood calcium levels. It may cause high levels of calcium in your urine, possibly resulting

in kidney stones. We do not know if Tymlos may worsen kidney stones in people who have had kidney stones before. For these reasons, we check your calcium levels before the study.

During animal drug testing, abaloparatide caused some rats to develop a bone cancer called osteosarcoma. It is not known if people who take abaloparatide will have a higher chance of getting osteosarcoma. Tell your study doctor or healthcare provider right away if you have pain in your bones, pain in any areas of your body that does not go away, or any new or unusual lumps or swelling under your skin that is tender to touch.

Tymlos may also have unforeseeable risks not mentioned. There is a risk of developing an immune reaction to the medication, such as rash, swelling, or anaphylaxis.

CT scans have a risk of radiation exposure. This study uses a CT scan of the cervical spine for research purposes only and it is not considered a necessary part of the routine care of cervical spine fractures. This is a repeat of the same CT scan you had following your injury that enabled your doctor to visualize your fracture. The radiation dose of the CT scan you will obtain is about 3 mSv (millisieverts, pronounced mil-e-see-verts). This radiation exposure equals the average yearly background radiation in the United States. Everyone receives background radiation naturally, which comes from outer space and from rocks and minerals in the soil. A radiation dose of 3 mSv is considered small and is associated with a very low risk of getting cancer later in life.

Blood work will be done at the study visits. The needle stick may hurt. There is a small risk of bruising, a rare risk of infection, and you may feel lightheaded.

DEXA scans have a risk of radiation exposure. The radiation dose of a DEXA scan is similar to the radiation dose of a single x-ray of your hand. The dose is much smaller than the x-ray you had for your neck fracture.

Incidental Findings

There is a possibility that while reviewing your blood work or imaging we may see an abnormality that may have health implications that we did not expect to see. This is what is called an “incidental finding.”

If we see an incidental finding, a qualified person (usually a member of the research team) will communicate the information to you. If you wish, we will provide information about this incidental finding to your primary doctor or we will refer you to an appropriate doctor for further evaluation.

This study is neither designed nor intended to detect health problems. The imaging that you will have as part of this research study does not substitute for an appropriate medical examination by a qualified health care provider. If you suspect that you might be suffering from injury or illness, you should not rely on this study as a way to determine your health status. The information from imaging will not be shared with you or your personal physician, unless (as mentioned above) there is an incidental finding.

An incidental finding may cause you to feel anxious. If you have further tests done, those results will then become part of your medical record, which may affect current and future health or life insurance. The costs for any care that will be needed to diagnose or treat an

incidental finding would not be paid for by this research study. These costs would be your responsibility.

What Are The Benefits of Participating In The Study?

This study is being carried out because it is unknown whether the study drug, Tymlos, will help improve the healing of your fracture or not. While we do not know if Tymlos will improve your fracture healing, your participation may potentially indirectly benefit patients in the future if the knowledge gained allows the medical community to expand its treatment for fractures in the elderly and to minimize the use of high-risk surgery in older adults with dens fractures.

During this study you will receive Tymlos, which is currently FDA approved medication for osteoporosis in postmenopausal women that may or may not be of benefit to you. Many patients with dens fractures have osteoporosis. If you have osteoporosis, the study drug, Tymlos, may reduce your risk of fractures in future.

What Other Options Are There?
If you decide not to participate, the standard treatment for your dens fracture will be recommended to you. This treatment is with a hard collar for 12 weeks WITHOUT the 8 weeks of the study drug (Tymlos).

Are There Any Costs?
There is no additional cost to participate in this study.

The study drug Tymlos is provided by the study at no cost to you. The DEXA bone scan (if required), research blood tests and the final 12-week CT scan are all paid for by the study. There are no other added expenses involved in study participation, other than those involved in transportation to the clinic, hospital or lab.

These study visits will also include elements of usual clinical care. Standard testing and treatment will be billed to you or your insurance. If standard care expenses are not covered by your insurance, you would be responsible for payment of those expenses.

What Is the Compensation?
You will not receive payment for participation in this study.

Can You Withdraw or Be Withdrawn From This Study?
You may discontinue your participation in this study at any time for any reason you choose. If you decide to stop, please let the research team know. If you decide to withdraw, your health care will not be affected and the standard of care treatment for your fracture will continue.

In addition, the principal investigator may discontinue your participation in this study at any time if you cannot follow the research plan or have side effects that the research team considers unsafe. If your fracture moves significantly, causes an increase in pain or disability, or your physician feels that this treatment is no longer in your best interest, the treatment will be stopped. If you are withdrawn from the study, you will receive the standard treatment for your fracture, and the data collected, such as medical notes, x-ray and CT images, lab values, and physical exam may be used in the final analysis of this study. There is no consequence from leaving the study.

If any new information becomes available that might affect your willingness to participate in the study, you will be informed of this information as soon as possible.

What About Confidentiality of Your Health Information?

Your health information is being used for your participation in this research protocol. We need to know your past medical history to ensure that it is safe for you to participate and we need to collect ongoing health information once you have begun the research study to ensure your continued safety and to determine what effect the research project has had on your diagnosis.

What health information will be used and disclosed for this study?

The health information we plan to collect for this study is listed below.

- Medical history and examinations
- Information that identifies you, such as your name, address, age, and sex
- Reports from hospital and clinic visits
- Laboratory and other test results
- X-ray and other images and reports
- Lists of medications you are taking
- Responses to health surveys and questionnaires
- Genetic testing results

Who is disclosing your health information for this research study?

- The University of Vermont Medical Center
- Other doctors' offices and hospitals where you may receive medical care while this study is active.

Who will use your health information in this study?

Our research team will use your health information. We may also share it with those who assist with the conduct of the research or oversight of the activities for this study. The representatives from the institutions, organizations, and agencies are listed below.

- The University of Vermont and its Committees on Human Research
- Officials from agencies and organizations that provide accreditation and oversight of research
- The University of Vermont Medical Center and the University of Vermont Larner College of Medicine
- Company(ies) that provide drugs or devices for this research project
- Federal and state agencies that oversee or review research information, such as the U.S. Food and Drug Administration (FDA), the Department of Health and Human Services, the National Institutes of Health, and public health and safety authorities
- Your health insurer, for portions of the research and related care that are considered billable

Your health information is protected by a federal law called the Health Information Portability and Accountability Act (HIPAA). Once your health information is shared outside of the University of Vermont Medical Center, we cannot guarantee that these laws will continue to apply. As a result, your health information could be further disclosed for other purposes. In the absence of a Certificate of Confidentiality, it is also possible for a court or other government

official to order the release of study data. The confidentiality of your health information cannot be guaranteed if you agree it may be used in this study.

How long will your health information be used for this research?
Your permission to use your health information will not end unless you withdraw your permission. If you are withdrawn from the study, data collected for the study before that point may be used in the final analysis of this study. During this study, you will not have access to study data. You may ask for your data once study activities are complete. You have a right to receive a copy of the information in your medical record at any time.

What if you decide not to give permission for research use of your health information?
If you decide not to allow the use and disclosure of your health information, you may not take part in this study. Your decision will have no effect on your current or future medical care.

If you choose to stop taking part in this study in the future, you may cancel permission for the use of your health information. You should let the research team know that you are cancelling your permission. A member of the research team will assist you in making your decision effective. The study will continue to use the health information already collected for the study before you cancelled your permission, and you cannot get back information that was already shared with others.

Who can answer your questions about the use and disclosure of your health information?
If you have questions or concerns about the use and disclosure of your health information, you should ask a member of the study team at (802) 656-8396 or the Privacy Officer at The University of Vermont Medical Center, Inc, at (802) 847-2667.

Safeguarding Your Health Information
A record of your progress will be kept in a confidential form at The University of Vermont Larner College of Medicine. The security of your study information will be maintained by the research team. The results of this study may eventually be published and information may be exchanged between medical investigators, but patient confidentiality will be maintained.

If your record is used or disseminated for government purposes, it will be done under conditions that will protect your privacy to the fullest extent possible consistent with laws relating to public disclosure of information and the law-enforcement responsibilities of the agency.

Please note that email communication is neither private nor secure. Though we are taking precautions to protect your privacy, you should be aware that information sent through e-mail could be read by a third party.

Clinical Trials Registration
A description of this clinical trial will be available on *http://www.ClinicalTrials.gov*, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

What Happens If You Are Injured?

If you are injured or become ill as a result of being in this research, The University of Vermont Health Network Affiliate hospital where you are enrolled in this research, will provide reasonable and usual medical care for that injury or illness. There will be no cost to you if the conditions listed below apply to your injury or illness. These conditions are:

1. The investigator determines that your injury or illness results from the research and not from your underlying condition or its usual treatment.
2. You let the investigator know about the injury or illness when you first notice it; and
3. You follow medical advice about proper treatment options for the injury or illness.

If the above conditions are not met, The University of Vermont Health Network affiliate hospital where you are seeking care may claim payments for your medical treatment from the study sponsor or your insurance company when these payments are allowed. If we bill your insurance for this care, you will be responsible for any associated co-payments or deductibles.

For an injury or illness that results from being in this study, The University of Vermont Health Network affiliate hospital where you are receiving care will not offer you any other payments, such as lost wages or expenses, except for your medical care. Even though you may receive medical care at no cost to you under certain conditions if you are in this study, The University of Vermont Health Network affiliate hospital and the University of Vermont do not admit to any responsibility for an injury or illness that results from being in the study.

If you agree to take part in this study and you sign this consent form, you are not giving up any of your legal rights.

Contact Information

You may contact Dr. David Lunardini the Investigator in charge of this study, at 802-847-2663 (802-847-BONE) for more information about this study. If you have any questions about your rights as a participant in a research project or for more information on how to proceed should you believe that you have been injured as a result of your participation in this study you should contact the Director of the Research Protections Office at the University of Vermont at 802-656-5040.

Statement of Consent

You have been given and have read or have had read to you a summary of this research study. Should you have any further questions about the research, you may contact the person conducting the study at the address and telephone number given below. Your participation is voluntary and you may refuse to participate or withdraw at any time without penalty or prejudice to your present and/or future care.

You agree to participate in this study and you understand that you will receive a signed copy of this form.

_____ _____

Signature of Subject Date

_____

Printed Name of Subject

_____

Signature of Principal Investigator or Designee Date

_____

Printed Name of Principal Investigator or Designee

Name of Principal Investigator: David Lunardini, MD
Department of Orthopaedics, University of Vermont
Burlington, VT 05403
802-847-2663 (802-847-BONE)

University of Vermont Consent to Participate in Research

Title of Research Project:	**Effect of PTH analog on union rates of Type II odontoid fractures in older adults**
Lead Investigator:	**David Lunardini, MD**
Sites Where Research is Being Conducted:	**University of Vermont Medical Center**
Sponsor:	**University of Vermont Larner College of Medicine**

Introduction

You are being invited to take part in this research study because you are over 50 years old and have broken a bone in your neck, called the dens, for which you completed a 12 week course of wearing a hard collar within the past 10 years. This study is being conducted by the University of Vermont at the UVM Medical Center.

Your participation in this research study is optional. We encourage you to ask questions and take the opportunity to discuss the study with anybody you think can help you make this decision.

Key Information to Help You Decide Whether or Not This Study Is Right for You

This is a research study to determine if an osteoporosis medication (Tymlos) can be used to improve healing of dens fractures. Tymlos is FDA-approved in the treatment of postmenopausal women with osteoporosis. It is commonly used to treat osteoporosis in men but is not FDA-approved for men specifically, nor is it currently FDA-approved as a treatment for dens fractures. If the fracture does not heal, it could lead to people having pain and disability. Most commonly, patients who don't heal experience neck pain. Less commonly, patients may develop weakness in the arms and legs or develop difficulty walking. Even with treatment in a rigid neck collar, on average the fracture only heals half of the time, with some reports finding that almost 9 out of 10 people do not heal the fracture. If this fracture does not heal, sometimes surgery is required. Surgery for this fracture carries many potential complications such as wound infection, bleeding, difficulty swallowing, and spinal cord injury. This is why we are studying the effect Tylmos on dens fracture healing.

We are testing two groups of people who will be wearing, or finished wearing, hard neck collars – people who take the Tymlos and people who did not. We will compare the amount of healing of dens fracture between the two groups.

You were previously given a hard collar to wear after fracture. You will NOT be asked to take a medication for this study. In this study, you will have a CT scan, which is a three dimensional form of x-ray, of your neck to measure how your fracture has healed. You might also have an x-ray to take a picture of your neck.

There is a risk associated with radiation exposure during a CT scan of your neck. This amount of radiation is small and similar to the amount of background radiation you are exposed to during one year of your regular life from the light from the sun.

The information above is only a brief summary of the study. If you are interested in learning more, it is important to read the following pages for additional detailed information about the study. If you decide to take part in the research, you will be asked to provide written consent at the end of this document.

Why Is This Research Study Being Conducted?

Dens fractures are the most common spine fractures in elderly people. Almost 9 out of 10 people over the age of 50 with these fractures do not end up healing because the bone does not grow back together. If this bone does not heal, people can have pain and disability, and sometimes these people end up needing surgery to help the bone heal, which can be dangerous. We would prefer another safer way to help the bone heal without surgery. One medication used in people with osteoporosis (thin bones), helps heal other broken bones in the body. We want to study if this medication can also help heal dens fractures.

What Is Involved In The Study?

You were previously treated with the routine treatment for dens fracture: a hard neck collar worn for 12 weeks. If you agree to be a part of this study, you will be asked to have a CT scan of your neck to measure the healing of your fracture. A CT scan will involve being placed on a table, and sliding into a tube to have pictures taken of the neck bones in three dimensions (3D). You might also be asked to have an x-ray. An x-ray involves sitting on a chair or stool, and having a picture taken of your neck bones from the side and the front. These images can be completed within approximately 1 hour. At the time of your imaging, we will also ask you to complete 2 paper questionnaires at the beginning of the study. These questionnaires will ask you about your neck symptoms and your ability to perform everyday activities. These questionnaires will take less than 10 minutes to complete. If you have severe pain, inability to move your head, neurologic problems, other debilitating signs or symptoms; or if your x-ray and CT scan show that your fracture is not healing, it may be recommended that you see an Orthopaedic Spine surgery specialist to discuss other treatment options.

The health information we plan to collect for this study is listed below.

- Medical history and examinations
- Information that identifies you, such as your name, address, age, and sex
- Reports from hospital and clinic visits
- Laboratory and other test results
- X-ray and other images and reports
- Lists of medications you are taking
- Responses to health surveys and questionnaires

Identifiable private information collected from you during this study may be used for future research studies or shared with other researchers for future research. Identifiable private information may be used for future research of many diseases or conditions. If the investigator distributes your information to other researchers or institutions, your information will be labeled with a research code so that you cannot be identified. No additional consent will be requested for the future research use of your samples or information collected from you during this study.

What Are The Risks and Discomforts Of The Study?

You will NOT be asked to take the study drug, Tymlos, if you decide to participate in this study.

If you decide to participate in this study, you will only be asked to have a neck x-ray if you did not previously have a flexion-extension neck x-ray 11 or more weeks after you began your hard collar treatment.

The CT scan does have risk of some radiation. This study uses a CT scan of the cervical spine for research purposes only and it is not considered a necessary part of the routine care of cervical spine fractures. This is also the same scan you had to help see the fracture after you were injured. The radiation dose of the CT scan you will obtain is about 3 mSv (millisieverts, pronounced mil-e-see-verts). This radiation exposure equals the average yearly background radiation in the United States. Everyone receives background radiation naturally, which comes from outer space and from rocks and minerals in the soil. A radiation dose of 3 mSv is considered small and is associated with a very low risk of getting cancer later in life.

Incidental Findings

There is a possibility that while reviewing your CT scan or x-rays we could see an abnormality that may have health implications that we did not expect to see. This is what is called an "incidental finding."

If we see an incidental finding, a qualified person (usually a member of the research team) will communicate the information to you. If you wish, we will provide information about this incidental finding to your primary doctor or we will refer you to an appropriate doctor for further evaluation.

This study is neither designed nor intended to detect health problems. The imaging that you will have as part of this research study does not substitute for an appropriate medical examination by a qualified health care provider. If you suspect that you might be suffering from injury or illness, you should not rely on this study as a way to determine your health status. The information from imaging will not be shared with you or your personal physician, unless (as mentioned above) there is an incidental finding.

An incidental finding may cause you to feel anxious. If you have further tests done, those results will then become part of your medical record, which may affect current and future health or life insurance. The costs for any care that will be needed to diagnose or treat an incidental finding would not be paid for by this research study. These costs would be your responsibility.

What Are The Benefits of Participating In The Study?

There is no direct benefit to you for participating in this study. Your participation could have a potential indirect benefit for patients in the future with fractures similar to yours, as information we get from this study may help inform treatment in the future for patients with similar neck fractures.

What Other Options Are There?

Participation in this study is voluntary. If you decide not to participate, your standard medical care will not be affected.

Are There Any Costs?
There are no other additional costs for this study, other than those involved in transportation to the hospital for imaging.

What Is the Compensation?
After your imaging and questionnaire responses have been collected for this study, you will receive $50.00 as compensation for your time and any inconvenience this study has caused you.

Can You Withdraw or Be Withdrawn From This Study?
You may discontinue your participation in this study at any time for any reason you choose. If you decide to stop, please let the research team know. If you decide to withdraw, your health care will not be affected, and the data collected, such as medical notes, x-ray and CT images, lab values, and physical exam may be used in the final analysis of this study.

If any new information becomes available that might affect your willingness to participate in the study, you will be informed of this information as soon as possible.

What About Confidentiality of Your Health Information?

Your health information is being used for your participation in this research protocol. We need to know your past medical history to ensure that it is safe for you to participate and we need to collect ongoing health information once you have begun the research study to ensure your continued safety and to determine what effect the research project has had on your diagnosis.

What health information will be used and disclosed for this study?
The health information we plan to collect for this study is listed below.

- Medical history and examinations
- Information that identifies you, such as your name, address, age, and sex
- Reports from hospital and clinic visits
- Laboratory and other test results
- X-ray and other images and reports
- Lists of medications you have taken
- Responses to health surveys and questionnaires

Who is disclosing your health information for this research study?

- The University of Vermont Medical Center
- Other doctors' offices and hospitals where you may receive medical care while this study is active.

Who will use your health information in this study?
Our research team will use your health information. We may also share it with those who assist with the conduct of the research or oversight of the activities for this study. The representatives from the institutions, organizations, and agencies are listed below.

- The University of Vermont and its Committees on Human Research
- Officials from agencies and organizations that provide accreditation and oversight of research

- The University of Vermont Medical Center and the University of Vermont Larner College of Medicine
- Company(ies) that provide drugs or devices for this research project
- Federal and state agencies that oversee or review research information, such as the U.S. Food and Drug Administration (FDA), the Department of Health and Human Services, the National Institutes of Health, and public health and safety authorities
- Your health insurer, for portions of the research and related care that are considered billable

Your health information is protected by a federal law called the Health Information Portability and Accountability Act (HIPAA). Once your health information is shared outside of the University of Vermont Medical Center, we cannot guarantee that these laws will continue to apply. As a result, your health information could be further disclosed for other purposes. In the absence of a Certificate of Confidentiality, it is also possible for a court or other government official to order the release of study data. The confidentiality of your health information cannot be guaranteed if you agree it may be used in this study.

How long will your health information be used for this research?
Your permission to use your health information will not end unless you withdraw your permission. If you are withdrawn from the study, data collected for the study before that point may be used in the final analysis of this study.

During this study, you will not have access to study data. You may ask for your data once study activities are complete. You have a right to receive a copy of the information in your medical record at any time.

What if you decide not to give permission for research use of your health information?
If you decide not to allow the use and disclosure of your health information, you may not take part in this study. Your decision will have no effect on your current or future medical care.

If you choose to stop taking part in this study in the future, you may cancel permission for the use of your health information. You should let the research team know that you are cancelling your permission. A member of the research team will assist you in making your decision effective. The study will continue to use the health information already collected for the study before you cancelled your permission, and you cannot get back information that was already shared with others.

Who can answer your questions about the use and disclosure of your health information?
If you have questions or concerns about the use and disclosure of your health information, you should ask a member of the study team at (802) 656-8396 or the Privacy Officer at The University of Vermont Medical Center, Inc, at (802) 847-2667.

Safeguarding Your Health Information
A record of your progress will be kept in a confidential form at The University of Vermont Larner College of Medicine. The security of your study information will be maintained by the research team. The results of this study may eventually be published and information may be exchanged between medical investigators, but patient confidentiality will be maintained.

If your record is used or disseminated for government purposes, it will be done under conditions that will protect your privacy to the fullest extent possible consistent with laws relating to public disclosure of information and the law-enforcement responsibilities of the agency.

Please note that email communication is neither private nor secure. Though we are taking precautions to protect your privacy, you should be aware that information sent through e-mail could be read by a third party.

University of Vermont Research Payment Information Requirement

You will be required to provide your name and address each time you receive a payment. You will also be requested to provide your social security number if the amount of the payment is $100 or if the total payments from UVM are equal to or greater than $600. If you are not a US Citizen or Permanent Resident Alien you will be required to complete additional paperwork including your immigration status for payment. This information will be strictly confidential and will be used for tax withholding and reporting purposes only and will allow the University to determine your US residency for federal income tax purposes.

Clinical Trials Registration

A description of this clinical trial will be available on *http://www.ClinicalTrials.gov*, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

What Happens If You Are Injured?

If you are injured or become ill as a result of being in this research, The University of Vermont Health Network Affiliate hospital where you are enrolled in this research, will provide reasonable and usual medical care for that injury or illness. There will be no cost to you if the conditions listed below apply to your injury or illness. These conditions are:

1. The investigator determines that your injury or illness results from the research and not from your underlying condition or its usual treatment.
2. You let the investigator know about the injury or illness when you first notice it; and
3. You follow medical advice about proper treatment options for the injury or illness.

If the above conditions are not met, The University of Vermont Health Network affiliate hospital where you are seeking care may claim payments for your medical treatment from the study sponsor or your insurance company when these payments are allowed. If we bill your insurance for this care, you will be responsible for any associated co-payments or deductibles.

For an injury or illness that results from being in this study, The University of Vermont Health Network affiliate hospital where you are receiving care will not offer you any other payments, such as lost wages or expenses, except for your medical care. Even though you may receive medical care at no cost to you under certain conditions if you are in this study, The University of Vermont Health Network affiliate hospital and the University of Vermont do not admit to any responsibility for an injury or illness that results from being in the study.

If you agree to take part in this study and you sign this consent form, you are not giving up any of your legal rights.

Contact Information
You may contact Dr. David Lunardini the Investigator in charge of this study, at 802-847-2663 (802-847-BONE) for more information about this study. If you have any questions about your rights as a participant in a research project or for more information on how to proceed should you believe that you have been injured as a result of your participation in this study you should contact the Director of the Research Protections Office at the University of Vermont at 802-656-5040.

Statement of Consent

You have been given and have read or have had read to you a summary of this research study. Should you have any further questions about the research, you may contact the person conducting the study at the address and telephone number given below. Your participation is voluntary and you may refuse to participate or withdraw at any time without penalty or prejudice to your present and/or future care.

You agree to participate in this study and you understand that you will receive a signed copy of this form.

_____ _____
Signature of Subject Date

_____
Printed Name of Subject

_____ _____
Signature of Principal Investigator or Designee Date

_____
Printed Name of Principal Investigator or Designee

Name of Principal Investigator: David Lunardini, MD
Address: 192 Tilley Drive, South Burlington, VT 05403
Telephone Number: 802-847-2663